

PATENT SPECIFICATION

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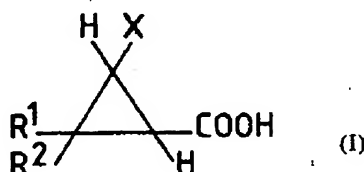


(54) PREPARATION OF CYCLOPROPANE DERIVATIVES

(71) We, SHELL INTERNATIONALE RESEARCH MAATSCHAPPIJ B.V., a Company organised under the laws of The Netherlands, of 30 Carel van Bylandtlaan, The Hague, The Netherlands, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

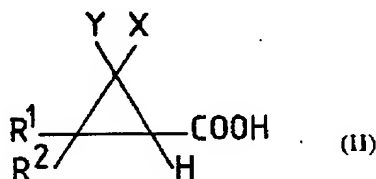
This invention relates to a process for the preparation of cyclopropane derivatives which are of particular interest as starting materials in the manufacture of agricultural chemicals related to the so-called "synthetic pyrethroids". The cyclopropane derivatives produced by the process according to the invention are novel compounds and are claimed as such.

Accordingly the present invention provides a process for the preparation of compounds having the following general formula:—



wherein

X is a halogen atom;
 R¹ is an alkyl group;
 R² is an alkyl group; or R¹ and R² together represent an alkylene chain;
 or a salt, anhydride, carboxamide or alkyl ester thereof, which comprises partially dehalogenating a cyclopropane-carboxylic acid of the following general formula:—



or a salt, anhydride, carboxamide or alkyl ester thereof, in the presence of zinc and an alkanolic acid, the symbols R¹, R² and X in formula II having the same meaning as in formula I and Y representing a halogen atom having an atomic number which is the same as or more than that of the halogen atom represented by X.

Preferred compounds prepared by the process according to the invention are those having general formula I wherein

X is a halogen atom;
 R¹ is an alkyl group of 1 to 6 carbon atoms;
 R² is an alkyl group of 1 to 6 carbon atoms; or

R¹ and R² together represent an alkylene chain of up to 5 carbon atoms; or the alkyl (1—6 carbon) esters, the alkali metal, alkaline earth metal and ammonium salts thereof.

In the general formula II when X represents a fluorine atom Y represents a fluorine, chlorine, bromine or iodine atom. When X represents a chlorine atom, Y represents a chlorine, bromine or iodine atom. When X represents a bromine atom, Y represents a bromine or an iodine atom and when X represents an iodine atom, Y also represents an iodine atom. X and Y are preferably equal and preferably represent chlorine atoms.

The substituents R¹ and R² are preferably both methyl groups.

Examples of preferred compounds of formula I are 3-chloro-2,2-dimethylcyclopropanecarboxylic acid, methyl 3-chloro-2,2-dimethylcyclopropanecarboxylate, and tert-butyl 3-chloro-2,2-dimethylcyclopropanecarboxylate.

The dehalogenation with zinc and an alkanolic acid is suitably carried out in the presence of an ammonium salt and/or water, because this enhances the conversion of the starting cyclopropane derivative; preferably, both an ammonium salt and water are present. Examples of ammonium salts are ammonium chloride and ammonium sulphate. Very good results have been obtained with ammonium chloride. The molar ratios of ammonium salt to zinc and of water to alkanolic acid are not critical and may vary within wide limits, but the best results are usually obtained at molar ratios ranging from 0.01:1 to 1:1.

The selectivity to the cyclopropanecarboxylic acid of the general formula I or to a salt, an anhydride, a carboxamide or an alkyl ester thereof is usually very high and often 100%, when use is made of a dehalogenating agent obtained by mixing zinc and an alkanolic acid for example acetic acid or propionic acid. The use of acetic acid has given very good results. The expression "selectivity to a certain compound", given in a percentage, is defined as:—

$$\frac{a}{b} \times 100$$

wherein a is the molar amount of the compound of formula II, or of a salt, an anhydride, a carboxamide or an alkyl ester thereof, converted into that certain compound, and b is the molar amount of the compound of formula II, or of a salt, an anhydride, a carboxamide or an alkyl ester thereof consumed in the course of the reaction.

The reaction temperature for the process according to the invention may lie within the range 50° to 150°C.

The conversion of the starting cyclopropane derivative is enhanced by carrying out the process under an atmosphere of an inert gas, such as nitrogen or a noble gas.

The molar ratio of zinc to the compound of formula II may vary within a wide range but is usually between 0.5:1 and 20:1, and preferably between 1:1 and 10:1. The zinc may be used in the form of dust, powder or granules. Zinc dust and powder are preferred, because small particles enhance the conversion of the compound of formula II and the proportion of the zinc used for the partial dehalogenation.

Simple derivatives of the carboxylic acid of formula I, e.g. the acyl halides, can be prepared from this acid in a manner known in the art.

As has been stated hereinbefore the products of the process according to the invention, i.e. the compounds of the general formula I are novel compounds and these are claimed as such.

The invention is further illustrated in the following Examples. The NMR spectra quoted were measured at 60 MHz using solutions of the compounds in deuteriochloroform.

Example I

Preparation of Methyl 3-Chloro-2,2-dimethylcyclopropanecarboxylate

A 500 ml, round-bottomed, three-necked flask, equipped with a mechanical stirrer, thermometer and reflux condenser, was charged with acetic acid, ammonium chloride and 0.1 mol of methyl 3,3-dichloro-2,2-dimethylcyclopropanecarboxylate. After the contents of the flask had been heated with stirring to reflux temperature — about 110°C — 0.46 mol of zinc powder was

gradually added over a period of 3 hours under an atmosphere of nitrogen. When the addition was complete the mixture was stirred under reflux for a period of 17 hours. At the end of this period the conversion of the starting methyl ester was 71% and the selectivity to the title ester 100%. Then 0.23 mol of zinc powder was added in one portion and stirring was continued for 7 hours. At the end of this period the conversion of the starting ester was 80% and the selectivity to the title ester 100%. Then 0.23 mol of zinc powder was added in one portion and stirring was continued for 16 hours, the molar ratio of ammonium chloride to the total amount of zinc added being 0.09. At the end of the latter period the selectivity to the title ester was 95% at 91% conversion of the starting ester. The molar ratios used were as follows:

acetic acid to methyl 3,3 - dichloro - 2,2 - dimethylcyclopropanecarboxylate	35:1
water to acetic acid	0.31:1
zinc to methyl 3,3 - dichloro - 2,2 - dimethylcyclopropanecarboxylate	9.2:1
ammonium chloride to zinc	0.09:1

The mixture obtained was allowed to adopt a temperature of 22°C and the unreacted zinc powder was recovered by decantation. The amount of zinc thus recovered corresponded to 74% of the starting amount. As 10% of the starting amount of the zinc had dechlorinated the starting methyl ester, 16% of the starting amount of the zinc had reacted with acetic acid, but had not been used for the dechlorination.

The decanted liquid obtained after the recovery of the unreacted zinc was poured out into 650 ml of water and the mixture of the organic and aqueous phases thus formed was extracted with three 50 ml portions of dichloromethane. The three extract phases were combined and the liquid thus obtained was washed with 100 ml of a saturated aqueous solution of sodium bicarbonate. The washed liquid was dried over anhydrous magnesium sulphate and the dichloromethane was removed from the dried liquid under reduced pressure. Fractional distillation of the residue at 18 mm Hg yielded the following three fractions:

Fraction	Boiling range, °C	starting methyl ester	Content of, %m, title ester	
			trans	cis
I	83—85	<5	71	24
II	85—87	8	82	8
III	87—90	16	>80	<4

The total yield of the title ester was 70%, calculated on starting methyl ester.

The NMR spectrum of the title ester showed the following absorptions relative to a tetramethylsilane standard:

the cis structure		the trans structure	
$\delta=1.22$ ppm (singlet, trans ¹¹ CH ₃)		$\delta=1.26$ ppm (singlet, trans ¹¹ CH ₃)	
$\delta=1.39$ ppm (singlet, cis ¹¹ CH ₃)		$\delta=1.35$ ppm (singlet, cis ¹¹ CH ₃)	
$\delta=1.79$ ppm (doublet, HCCOOCH ₃); I=7.8 Hz H—H		$\delta=1.77$ ppm (doublet, HCCOOCH ₃); I=4.2 Hz H—H	
$\delta=3.26$ ppm (doublet, HCCI); I=7.8 Hz H—H		$\delta=3.50$ ppm (doublet, HCCI); I=4.2 Hz H—H	
$\delta=3.71$ ppm (singlet, COOCH ₃)		$\delta=3.71$ ppm (singlet, COOCH ₃)	

¹¹with respect to the COOCH₃ group.

Example II

Preparation of 3-Chloro-2,2-dimethylcyclopropanecarboxylic Acid

The flask used in Example I was flushed with nitrogen and charged with acetic acid, water, ammonium chloride and 0.165 mol of 3,3 - dichloro - 2,2 - dimethylcyclopropanecarboxylic acid. After the contents of the flask had been heated to reflux temperature with stirring, zinc powder — originating from a bottle that had been opened for the first time — was gradually added over a period of 45 minutes. Then the flask was kept at this temperature for a period of 20 hours. The molar ratios used were as follows:

acetic acid to 3,3 - dichloro - 2,2 -
dimethylcyclopropanecarboxylic acid 32:1
water to acetic acid 0.31:1
zinc to 3,3 - dichloro - 2,2 -
dimethylcyclopropanecarboxylic acid 4.2:1
ammonium chloride to zinc 0.12:1

At the end of the latter period the selectivity to the title acid was 100% at 80% conversion of 3,3 - dichloro - 2,2 - dimethylcyclopropanecarboxylic acid.

The mixture obtained was allowed to adopt a temperature of 22°C and the unreacted zinc powder was recovered by decantation. The amount of zinc thus recovered corresponded to 49% of the starting amount. As 19% of the starting amount of the zinc had dechlorinated the starting acid, 32% of the starting amount of the zinc had reacted with acetic acid, but had not been used for the dechlorination.

The acetic acid was flashed off from the decanted liquid obtained after recovery of the zinc powder at a pressure of 12 mm Hg and the residue obtained was mixed with 200 ml of water. The mixture formed was extracted with five 50 ml portions of dichloromethane, the five extract phases were combined, the liquid thus obtained was dried over anhydrous magnesium sulphate and the dichloromethane was removed from the dried liquid under reduced pressure. Fractional distillation of the residue yielded the following four fractions:

Fraction	Boiling point, °C	Pressure, mm Hg	acetic acid	Content of, %m,		
				starting acid	trans	cis
I	50—55	0.2	98	0	1	1
II	78	0.05	1	12	31	45
III	85	0.15	0	17	27	56
IV	85	0.15	0	24	17	59

The total yield of the title acid was 62%, calculated on starting 3,3 - dichloro - 2,2 - dimethylcyclopropanecarboxylic acid.

The NMR spectrum of the title acid showed the following absorptions relative to a tetramethylsilane standard:

the cis structure		the trans structure	
$\delta=1.24$ ppm (singlet, trans" CH ₃)		$\delta=1.32$ ppm (singlet, trans" CH ₃)	
$\delta=1.40$ ppm (singlet, cis" CH ₃)		$\delta=1.39$ ppm (singlet, cis" CH ₃)	
$\delta=1.78$ ppm (doublet, HCCOOCH ₃)		$\delta=1.77$ ppm (doublet, HCCOOCH ₃);	
l=7.9 Hz H—H		l=4.1 Hz H—H	
$\delta=3.28$ ppm (doublet, HCCl);		$\delta=3.51$ ppm (doublet, HCCl);	
l=7.9 Hz H—H		l=4.1 Hz H—H	
$\delta=11.1$ ppm (singlet, COOH)		$\delta=11.1$ ppm (singlet, COOH)	

"with respect to the COOH group.

Examples III—VII

Preparation of 3-Chloro-2,2-dimethylcyclopropanecarboxylic Acid

A 100 ml, round-bottomed, three-necked flask, equipped with a magnetic stirrer, thermometer and reflux condenser was charged with 3,3 - dichloro - 2,2 - dimethylcyclopropanecarboxylic acid, water, ammonium chloride, if any, and zinc. The flask had not been flushed with nitrogen. The contents of the flask were heated with stirring to reflux temperature and kept at this temperature for a certain period. At the end of this period the conversion of 3,3 - dichloro - 2,2 - dimethylcyclopropanecarboxylic acid and the selectivity to the title acid were determined. Two of the molar ratios used were as follows:

acetic acid to 3,3 - dichloro - 2,2 - dimethylcyclo-
propanecarboxylic acid 32:1
zinc to 3,3 - dichloro - 2,2 - dimethylcyclopropane-
carboxylic acid 4.2:1

Five experiments were carried out in the manner described above. The Table shows the starting amount of 3,3 - dichloro - 2,2 - dimethylcyclopropanecarboxylic acid, the molar ratio of water to acetic acid and of ammonium chloride to zinc, the type of zinc used, the reaction time and the conversion of 3,3 - dichloro - 2,2 - dimethylcyclopropanecarboxylic acid at the end of this type. The selectivity to the title acid was 100% in the five experiments.

TABLE

Example	Starting amount of 3,3-dichloro- 2,2-dimethylcyclo- propanecarboxylic acid, mol	Molar ratio water to acetic acid	NH ₄ Cl to zinc	Type of zinc used	Reaction time, h	Conversion of 3,3-dichloro- 2,2-dimethyl- cyclopropane- carboxylic acid, %	Zinc, % of starting amount reacted	not for de- chlorination
III	0.022	0.31:1	0:1	powder	6	32	78	8
IV	0.011	0.94:1	0:1	ditto	22	39	75	10
V	0.011	0.31:1	0.12:1	ditto	21	61	82	15
VI	0.011	0.31:1	0.61:1	ditto	20	42	58	10
VII	0.011	0.31:1	0.12:1	20 mesh ¹⁾	1.5	9	19	2

¹⁾U.S. Sieve Series A.S.T.M. -E-11-61, largest dimension of particles being 0.841 mm.

At the end of the reaction time the mixtures were allowed to adopt a temperature of 22°C and the unreacted zinc was recovered by decantation. The amounts of zinc recovered, used for dechlorination and reacted but not used for dechlorination, are also presented in the table.

Example VIII

Preparation of 3-Chloro-2,2-dimethylcyclopropanecarboxylic Acid
The flask used in Example III was charged with 0.018 mol of tert-butyl 3,3-dichloro-2,2-dimethylcyclopropanecarboxylate, acetic acid and zinc powder. The molar ratios used were as follows:

acetic acid to tert-butyl 3,3-dichloro-2,2-dimethylcyclopropanecarboxylate	39:1
zinc to tert-butyl 3,3-dichloro-2,2-dimethylcyclopropanecarboxylate	5:1

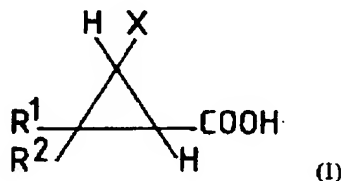
The contents of the flask were heated with stirring to reflux temperature and kept at this temperature for 18 hours. After 30 minutes' heating the tert-butyl ester had been quantitatively converted into 3,3-dichloro-2,2-dimethylcyclopropanecarboxylic acid. At the end of the period of 18 hours the selectivities were as follows:

to 3,3-dichloro-2,2-dimethylcyclopropanecarboxylic acid	80%
to 3-chloro-2,2-dimethylcyclopropanecarboxylic acid	10%
to organic compounds with an open chain of carbon atoms	10%

Comparison of the conversion of 3,3-dichloro-2,2-dimethylcyclopropanecarboxylic acid — which was only 20% — and the selectivity to 3-chloro-2,2-dimethylcyclopropanecarboxylic acid of this example with those of Example III shows the favourable effect of water.

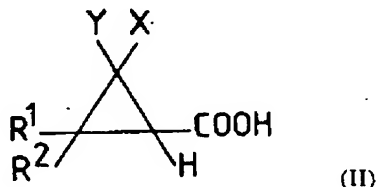
WHAT WE CLAIM IS:—

1. A process for the preparation of compounds having the following general formula:—



wherein

X is a halogen atom;
R¹ is an alkyl group;
R² is an alkyl group; or R¹ and R² together represent an alkylene chain;
or a salt, anhydride, carboxamide or alkyl ester thereof, which comprises partially dehalogenating a cyclopropane-carboxylic acid of the following general formula:—



or a salt, anhydride, carboxamide or alkyl ester thereof, in the presence of zinc and an alkanolic acid, the symbols R¹, R² and X in formula II having the same meaning

as in formula I and Y representing a halogen atom having an atomic number which is the same as or more than that of the halogen atom represented by X.

2. A process according to Claim 1, wherein in formula I:—

X is a halogen atom;

R¹ is an alkyl group of 1 to 6 carbon atoms;

R² is an alkyl group of 1 to 6 carbon atoms; or

R¹ and R² together represent an alkylene chain of up to 5 carbon atoms; or the alkyl (1—6 carbon) esters, the alkali metal, alkaline earth metal and ammonium salts thereof.

3. A process according to Claim 1 or 2, wherein X and Y are chlorine and R¹ and R² are both methyl groups.

4. A process according to any one of the preceding claims, wherein dehalogenation is achieved with zinc and an alkanolic acid in the presence of an ammonium salt.

5. A process according to Claim 4 carried out in the additional presence of water.

6. A process according to Claim 5, wherein the molar ratios of ammonium salt to zinc and of water to alkanolic acid are in the range 0.01:1 to 1:1.

7. A process according to Claims 4, 5 or 6, wherein the alkanolic acid is acetic or propionic acid.

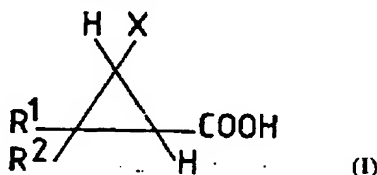
8. A process according to any one of the preceding claims, wherein the molar ratio of zinc to the compound of formula II is in the range 0.5:1 to 20:1.

9. A process according to Claim 1, wherein 2,2 - dihalo - 3,3 - dimethylcyclopropanecarboxylic acid or its lower alkyl ester is partially dehalogenated in the presence of zinc, acetic acid, an ammonium salt and water to give 2 - halo - 3,3 - dimethylcyclopropanecarboxylic acid or its lower alkyl ester.

10. A process for the preparation of compounds having the general formula I substantially as hereinbefore described and with reference to any one of Examples.

11. A compound of formula I prepared by a method claimed in any one of the preceding claims.

12. A compound of the following general formula:—



wherein

X is a halogen atom;

R¹ is an alkyl group;

R² is an alkyl group; or R¹ and R² together represent an alkylene chain; or a salt, anhydride, carboxamide or alkyl ester thereof.

13. A compound according to Claim 12, wherein

X is a halogen atom;

R¹ is an alkyl group of 1 to 6 carbon atoms;

R² is an alkyl group of 1 to 6 carbon atoms; or

R¹ and R² together represent an alkylene chain of up to 5 carbon atoms; or an alkyl (1—6 carbon) ester, or alkali metal, alkaline earth metal or ammonium salt thereof.

14. A compound according to Claim 12 or 13, wherein X and Y are chlorine and R¹ and R² are both methyl groups.

15. A compound according to Claim 12 specifically named herein.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP2004/000018

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl⁷ C07C67/317, 69/74, C07B61/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl⁷ C07C67/317, 69/74, 51/377, 61/15, C07B61/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CA (STN), REGISTRY (STN), CASREACT (STN), BEILSTEIN (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 6-157418 A (Daiichi Pharmaceutical Co., Ltd.), 03 June, 1994 (03.06.94), (Family: none)	1-10
A	WO 95/4712 A1 (Daiichi Pharmaceutical Co., Ltd.), 16 February, 1995 (16.02.95), & EP 712831 A1 & US 5780669 A & JP 7-97353 A	1-10
A	GB 1594224 A (SHELL INTERNATIONALE RESEARCH MAATSCHAPPIJ B.V.), 30 July, 1981 (30.07.81), & DE 2802967 A1 & JP 53-92743 A	1-10

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

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Date of the actual completion of the international search
01 April, 2004 (01.04.04)

Date of mailing of the international search report
20 April, 2004 (20.04.04)

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